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Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Via Federal Express

WARNING LETTER

Peter N. Arrowsmith, M.D.
Arrowsmith Eye Institute
210 25th Avenue, North, Suite 900
Nashville, Tennessee 37203

Dear Dr. Arrowsmith:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site and to request your prompt reply informing us of your corrective actions. During the period of October 6 through October 7, 2003, Ms. Patricia S. Smith, an investigator from the FDA's New Orleans District Office, visited you. The purpose of that visit was to conduct an inspection to determine whether your activities and procedures as a clinical investigator for the investigational study of the [REDACTED] for the correction of high myopia in phakic eyes, sponsored by [REDACTED], complied with applicable FDA regulations. This product is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), or Premarket Notification (510(k)) submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report submitted by the New Orleans District Office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemptions and Part 50-Protection of Human Subjects, and Section 520(g) of the Act. At the conclusion of the inspection, Ms. Smith presented and discussed with you the observations listed on the Form FDA 483 "Inspectional Observations." [REDACTED], was also present.

The deviations noted on the Form FDA 483 and our subsequent review of the inspection report are discussed below. The deviations noted include:

Failure to obtain informed consent (21 CFR 812.140(a)(3)(i), and 21 CFR 812.100).

A review of patient records for all 45 study subjects enrolled in the [REDACTED] revealed the following:

- At least one subject [REDACTED] failed to sign the correct informed consent form prior to the study procedure. The procedure date was 2/19/03, but the subject did not sign the consent form until 9/12/03.
- No consent form was observed for one subject [REDACTED] for the initial procedure that took place on 8/12/99.
- The 5/18/99 version of the informed consent form was not written in language that would necessarily be understandable to subjects or their representatives. Terms such as *loss of corneal clarity, retinal detachment, glaucoma, Keratomileusis, corneal inlays, and corneal rings* were not defined in the form.
- At least one subject signed a study procedure-related consent form that was not approved by the Institutional Review Board (IRB) and that did not meet the required elements of the applicable regulations. For example, the consent entitled, "Addendum to the Patient Informed Consent for [REDACTED]" lacked an explanation of whom to contact for answers to pertinent questions regarding subjects' rights or study related injuries.
- One subject ([REDACTED]) signed a 10/9/97 version of the informed consent form on 5/18/99. That form was outdated by that time and had been replaced by a newer version.

For your information, informed consent must be obtained from the subject or the subject's legally authorized representative prior to his or her participation in an investigational study, in accordance with 21 CFR Part 50. This includes obtaining the subject's or the legally authorized representative's signature indicating that the study subject has been informed of the risks and benefits of participating in the clinical trial (21 CFR 50.27).

Failure to prepare and submit complete, accurate, and timely reports to the sponsor and IRB (21 CFR 812.150(a)(1) and 812.150(a)(3)).

You failed to submit complete, accurate and timely reports to the study sponsor and the reviewing IRB. For example:

- Adverse Reaction Reports were filed with the sponsor for subjects [REDACTED] and [REDACTED]. However, there is no documentation that the Western Institutional Review Board (WIRB) was notified of the adverse events that occurred at your site.

Nonetheless, the most recent WIRB Continuing Review Report completed and signed by [REDACTED] on 8/16/03 indicated there were no unexpected adverse events at your site which had not previously been reported to the IRB.

- In addition, the 8/16/03 WIRB Continuing Review Report indicated there were no withdrawals from the study. However, a review of patient's records revealed Early Termination Forms were completed for the following subjects:
 - [REDACTED] – termination date 10/10/01
 - [REDACTED] – termination date 11/10/02
 - [REDACTED] – termination date 4/11/01
 - [REDACTED] – termination date 11/23/02
 - [REDACTED] – termination date 9/7/01
- Adverse Reaction Reports to the sponsor were not completed and signed until dates much later than when the adverse events occurred. For example:
 - Subject [REDACTED] – adverse event occurred on 2/18/99, the Adverse Reaction Report was not completed and signed until 9/30/03, over 4 years later;
 - Subject [REDACTED] – adverse event occurred on 3/20/01, the Adverse Reaction Report was not completed and signed until 11/19/02; and
 - Subject [REDACTED] – adverse event occurred on 3/12/99, the Adverse Reaction Report was not completed and signed until 4/10/02.

FDA regulations require the submission of complete and accurate periodic progress reports on the investigation, at least yearly, to the sponsor, monitor, and reviewing IRB (21 CFR 812.150(a)(3)). FDA regulations also state that an investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)).

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist in connection with this clinical study. It is your responsibility as a clinical investigator to ensure that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations.

Within fifteen (15) working days of your receipt of this letter, please inform FDA of the corrective actions taken to remedy the deviations noted above. Failure to respond could result in regulatory action without further notice. Please send all information requested to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2094 Gaither Road, Rockville, Maryland 20850, Attention: Pamela M. Reynolds.

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A copy of this Warning Letter has been sent to FDA's New Orleans District Office, 6600 Plaza Drive, Suite 400, New Orleans, Louisiana 70127. We request that a copy of your response also be sent to the New Orleans District Office.

Please direct all questions concerning this matter to Ms. Pamela Reynolds at (301) 594-4723, ext. 155.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Michael E. Marcarelli".

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health